

ORDER TO CEASE MANUFACTURING, RECALL AND DESTROY HCT/Ps

November 5, 2012

HAND DELIVERED

Eli Gendler, M.D./Ph.D.
Medical Director
Pacific Coast Tissue Bank
2400 S Flower Street, 5th floor
Los Angeles, CA 90007-2631

Dear Dr. Gendler:

Your firm Pacific Coast Tissue Bank (or Establishment), located at 2400 S Flower Street, Los Angeles, CA, manufactures human cells, tissues, and cellular and tissue-based products (HCT/Ps). The Food and Drug Administration (FDA or Agency) conducted an inspection of your Establishment between April 24 and June 19, 2012, and at the conclusion of the inspection, the FDA investigator issued to you¹ a Form FDA-483, Inspectional Observations. Our review of the information and records examined and collected during the inspection revealed significant violations by Pacific Coast Tissue Bank of Title 21, Code of Federal Regulations, Part 1271 (21 CFR 1271), issued under the authority of Section 361 of the Public Health Service Act (PHS Act) [42 United States Code (USC) 264]. The agency has therefore determined that you do not provide adequate protections against the risks of communicable disease transmission due to these serious violations of 21 CFR 1271. The Agency has also determined that there are reasonable grounds to believe the HCT/Ps manufactured by your Establishment pose a danger to health, and, accordingly, this Order to Cease Manufacturing is effective immediately. HCT/Ps subject to this Order will be recalled and destroyed within five (5) working days from the date of receipt of this Order. FDA retains authority to pursue other actions and remedies.

Therefore, pursuant to 21 CFR 1271.440(a)(1) and (3), you must:

1. Immediately cease all manufacturing of HCT/Ps until compliance with the regulations in 21 CFR 1271 has been achieved and you have been provided written authorization from FDA to resume operations. Under 21 CFR 1271.3(e), manufacture means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any HCT/P, and the screening or testing of the HCT/P donor;

¹ Throughout this order, “you” refers both to the Establishment, and/or you personally, as well as in your capacity as Medical Director and Owner of the Establishment, as appropriate.

2. Destroy all HCT/Ps that are in your possession; and
3. Within five (5) working days from the date of receipt of this order, recall and destroy all HCT/Ps distributed since March 19, 2009, the date you began manufacturing HCT/Ps.

Please forward your consignee/customer notification letter to the contact provided later in this Order for review and approval prior to sending to your consignees/customers.

We base this order on FDA's inspection, which was carried out between April 24 and June 19, 2012, and record review. As a result, the Agency noted significant noncompliance with the relevant federal regulations, including, but not limited to, the following violations, some of which date back to the time you began manufacturing:

A. CURRENT GOOD TISSUE PRACTICE

Receipt and Distribution

1. Failure to evaluate each incoming HCT/P for the presence and significance of microorganisms and inspect for damage and contamination. You must determine whether to accept, reject, or place in quarantine each incoming HCT/P, based upon pre-established criteria designed to prevent communicable disease transmission [21 CFR 1271.265(a)]. Specifically:

You do not perform pre-processing cultures on bone HCT/Ps received from the recovery organization to determine the presence or significance of microorganisms prior to processing.

2. Failure to review manufacturing and tracking records pertaining to the HCT/P, and, on the basis of that record review, verify and document that the release criteria have been met [21 CFR 1271.265(c)(1)]. Specifically:

You received pre-processing culture results from the recovery organization, for donors whose skin & cardiovascular tissues tested positive for highly pathogenic organisms. You also received HCT/Ps (bone) recovered from these same donors. You determined that the HCT/Ps (bone) were acceptable for processing and distribution. HCT/Ps from the following donors were distributed: Donor -(b)(6)-(*Clostridium perfringens*); Donor -(b)(6)- (*Clostridium sordellii*); Donor -(b)(6)- (*Clostridium septicum*); Donor -(b)(6)- (*Escherichia coli*); Donor -(b)(6)- (*Filamentous Fungi*), Donor -(b)(6)- (*Fungus isolated*), and Donor -(b)(6)- (*Staphylococcus aureus*).

3. Failure to establish and maintain procedures, including release criteria, for activities relating to the receipt of HCT/Ps [21 CFR 1271.265(e)]. Specifically:

Your SOPs do not include the evaluation of pre-processing cultures for incoming HCT/Ps received from recovery organizations for the presence and significance of microorganisms and inspection for damage and contamination.

4. Failure to establish and maintain procedures to determine if an HCT/P that is returned to the establishment is suitable to be returned to inventory [21 CFR 1271.265(f)]. Specifically:

You do not have procedures for determining if HCT/Ps that are returned to your firm are suitable to be returned to inventory. From 3/31/10 to 4/5/12, 84 HCT/Ps from various product lines were returned to inventory without an evaluation for the presence of microorganisms, damage, or contamination. You stated that the reasons for returning HCT/P products are kept inside your head and are never documented.

Process Validation

1. Failure to validate and approve a process according to established procedures where the results of processing cannot be fully verified by subsequent inspection and tests [21 CFR 1271.230(a)]. Specifically:
 - a. There is no documentation of validation of the -----(b)(4)----- process.
 - b. With the exception of the ----(b)(4)---- process, there is no documentation of validation of the processing steps for the Lambone, Dembone, and Osteomin demineralized bone products.
2. Procedures to validate and approve processes that cannot be fully verified by subsequent inspection and tests were not defined and implemented [21 CFR 1271.230(a)]. Specifically:
 - a. Your firm employed a contractor to conduct process validation for the ----(b)(4)---- of three product lines (Dembone, Lambone, and Osteomin). However, the validation was designed for medical devices and did not adequately evaluate incoming bioburden for HCT/Ps, which by their very nature are more variable. In addition, the limited bioburden evaluation did not address anaerobic microorganisms such as *Clostridium sp.* You accepted, processed, and distributed HCT/Ps from a donor who tested positive for *Clostridium sp.*
 - b. Your firm labels the Dembone, Lambone, and Osteomin demineralized bone products as “Sterile” following -----(b)(4)----- . The final validation report for the ----(b)(4)---- process requires ----(b)(4)---- audits, which include bioburden assessments and review of environmental monitoring data. These ----(b)(4)---- are essential to substantiate the continued ability of an ----(b)(4)---- process to prevent the introduction, transmission, or spread of communicable diseases. However, you have not adhered to a ----(b)(4)---- audit schedule since the ----(b)(4)---- process was originally validated.

Processing and Process Controls

Failure to process each HCT/P in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P [21 CFR 1271.220(a)]. Specifically:

Your processes for the Lambone, Dembone, and Osteomin demineralized bone products do not include in-process controls, such as pre-processing² and post-processing/pre---(b)(4)---- cultures.

Environmental Control and Monitoring

1. Failure to adequately control environmental conditions and provide proper conditions for operations, where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment. Where appropriate, you must provide for cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations [21 CFR 1271.195(a)(3)]. Specifically:

The FDA investigator observed the following:

- a. An unclean rag, full of dust and other filth, was found on top of the laminar flow hood in the Processing area, where HCT/Ps are exposed overnight to ambient air.
 - b. A dead bug was found on top of the laminar flow hood in the Processing area (Room (b)(4)).
 - c. A worn, yellow sponge is used for cleaning a sink and washing glassware that is used during processing. The sponge is used until it begins to unravel or the dedicated cleaning person feels the need to change it.
 - d. Three sponges attached to separate squeegee handles had dirt and grime build-up and are used daily to spread disinfecting solution over working counter surfaces and tables used to process and label HCT/Ps.
2. Failure to monitor environmental conditions where they could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment [21 CFR 1271.195(c)]. Specifically:
 - a. Your firm does not perform environmental monitoring in Room (b)(4), where manufacturing processes for your bone products are performed.
 - b. Your environmental monitoring program does not include monitoring for either viable air particles or personnel.

Equipment

1. Failure to clean, sanitize, and maintain equipment according to established schedules [21 CFR 1271.200(a)]. Specifically:

² See, e.g., Final Guidance for Industry, Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), Section XIII.D (Dec. 2011), available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM285223.pdf>.

- a. Your bone-cutting equipment (Serial # ----(b)(4)----, Model #---(b)(4)---) has a build-up of unidentified material embedded into the rear interior of the plastic lid. This equipment was last cleaned on 4/25/11.
 - b. Your firm covers cracks and seals holes in your bone-cutting equipment (Serial #-----
--(b)(4)-----, Model ----(b)(4)----) using what appears to be tape and epoxy. This equipment was last cleaned on 4/25/11.
2. Failure to establish and maintain adequate procedures for cleaning, sanitizing, and maintaining equipment to prevent malfunctions, contamination or cross-contamination, or accidental exposure of HCT/Ps to communicable disease agents [21 CFR 1271.200(b)]. Specifically:
 - a. Your firm has not established a procedure for maintenance of freezers, used to store HCT/Ps.
 - b. The air inlet filter, attached to the -----(b)(4)----- and used to filter the open air entering the -----(b)(4)----- during the -----(b)(4)----- process, had not been changed in two years. The filters were removed during the inspection. There is no procedure to address when filters should be replaced.

Facilities

1. Failure to maintain the processing facility in a good state of repair, adequate to prevent contamination of HCT/Ps [21 CFR 1271.190(a)]. Specifically:

The FDA investigator observed the following:

- a. Numerous water-stained ceiling tiles were located above HCT/P processing surfaces.
 - b. An accumulation of dust and dirt on piping attached to the storage area ceiling directly above an open box of gowns, used during processing of HCT/Ps.
 - c. Red and black duct tape is used to secure cracked sections of a damaged light fixture, located directly above a work surface where bone washing is performed.
 - d. Two holes in a section of ceiling where HCT/Ps are exposed to ambient air overnight.
2. Failure to document, and maintain records of, all cleaning and sanitation activities performed to prevent contamination of HCT/Ps [21 CFR 1271.190(d)(2)]. Specifically:

A review of processing records from January 2009 to May 2012 revealed approximately 148 occasions when daily cleaning and sanitation of counter surfaces and tables was not documented. HCT/Ps from at least (b)(4) donors were processed during this time.

Complaint File

Failure to maintain a record of complaints received in a file designated for complaints [21 CFR 1271.320(b)]. Specifically:

A review of customer files found a complaint consisting of two tracking records, which involved several vials of laminar bone tissue (Donor lot #---(b)(6)---) that had no vacuum, which could cause contamination of the HCT/P. These records were not maintained in the file designated for complaints.

B. ADDITIONAL REQUIREMENTS FOR ESTABLISHMENTS

Reporting

1. Failure to investigate all HCT/P deviations related to a distributed HCT/P for which the firm performed a manufacturing step [21 CFR 1271.350(b)(1)]. Specifically:

You did not conduct investigations into complaints involving loss of vacuum in vials of Lambone product. Tracking records revealed implantation of bone products from the implicated lots.

2. Failure to report an HCT/P deviation relating to the core CGTP requirements [21 CFR 1271.350(b)(2)]. Specifically:

You failed to report to FDA the loss of vacuum, which could cause contamination of the HCT/P, in several vials of Lambone 83cx product.

On July 3, 2012, FDA received your written response, dated July 2, 2012, to the Form FDA 483, List of Inspectional Observations, issued to Pacific Coast Tissue Bank at the close of the inspection. We have reviewed the corrective actions outlined in the response and we have determined that they are inadequate to address our concerns. Your response addresses only prospective changes related to the observations cited during the inspection. You did not discuss how you plan to address the HCT/Ps that were processed in your facility since March 19, 2009 and are in violation of 21 CFR 1271. We also have specific comments regarding your response, as follows:

1. Your response to Observation 1 states, "...tissues (dermis and saphenous veins) were recovered and packaged separately and were not in contact or comingled with bone...Therefore tissues with positive cultures listed in the observations were not present at any time on the premises of the Pacific Cast [sic] Tissue Bank, nor were they handled at any time by the Pacific Coast Tissue Bank Personnel." We note that while the positive cultures were reported for HCT/Ps other than those received by your establishment, they were recovered from the same donors from whom you also received and processed HCT/Ps. In addition, you did not perform pre-processing cultures on the HCT/Ps you received from the

recovery agency, therefore you have no documentation to support that those HCT/Ps were negative for microorganisms prior to processing.

Your response refers to FDA's Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) to justify your decision not to perform pre-processing cultures and to disregard the results of pre-processing cultures from recovery organizations, all based on your use of a terminal sterilization process validated to a sterility assurance level (SAL) of 10^{-6} . The Guidance provides that you: "...[N]ot process any musculoskeletal HCT/Ps from a donor that has any pre-processing cultures positive for *Clostridium*, *Streptococcus pyogenes* (group A strep), or any other microorganisms that you have determined to be difficult to eliminate, unless you have a terminal sterilization process validated to a sterility assurance level (SAL) of 10^{-6} ." This does not state that you can forego conducting pre-processing cultures if you perform the recommended terminal sterilization process. To the contrary, this statement is included as part of a discussion emphasizing the importance of conducting pre-processing cultures. However, as previously mentioned, you do not perform any pre-processing cultures, nor do you evaluate any pre-processing culture results received from any recovery organization. Furthermore, your terminal sterilization process was not adequately validated, including the fact that anaerobic microorganisms, such as *Clostridium sp.*, were not evaluated. Indeed, *Clostridium sp.* was found in pre-processing cultures for at least three donors from whom you also received HCT/Ps.

Under 21 CFR 1271.220(a), you must process each HCT/P in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction transmission or spread of communicable disease through the use of the HCT/P. This requirement is met through in-process control and testing under 21 CFR 1271.220(c). The CGTP Guidance discusses the importance of pre-processing cultures, in that they are considered a critical in-process control for musculoskeletal HCT/Ps and that all results for pre-processing cultures should be considered when determining whether to accept or reject incoming musculoskeletal HCT/Ps prior to processing. If musculoskeletal HCT/Ps are processed with a bioburden in excess of the level that a sterilization process has been validated to reduce or eliminate, there is no assurance that processing will reduce or remove bioburden to acceptable limits or reduce the risk of transmission of communicable disease risk. Pre-processing cultures play a critical role in monitoring the process input to ensure that the process capability will not be affected. Thus terminal sterilization should not be used as an alternative to performing pre-processing cultures. In addition, because you do not perform post-processing/pre----(b)(4)---- cultures or bioburden studies, the type or number of microorganisms on your products is unknown. Therefore, we cannot evaluate to what degree your terminal sterilization process minimizes the risk of communicable disease transmission.

2. Your response to Observation 2.B. does not commit to performing validation of all your processing steps used for the Lambone, Dembone, and Osteomin products. We note that process validation is a regulatory requirement and must be performed for all your processing steps. This requirement cannot be met through validation of only select processing steps, such as terminal ----(b)(4)----.

3. Your response to Observation 3 states, "Since bioburden is determined at the end of processing no 'preprocessing cultures' are performed." There is no evidence that your firm routinely performs bioburden testing (i.e. post-processing cultures) on HCT/Ps at the end of processing to determine the bioburden prior to the ----(b)(4)---- process.
4. In your response to Observation 4.A., you indicated that your firm has not manufactured the Lambone 83cx product since ----(b)(4)----, therefore ----(b)(4)---- audits could not be performed. We acknowledge that the Lambone 83cx has not been manufactured since ----(b)(4)----, thus ----(b)(4)---- audits could not be performed. You stated that you intend to begin production of this product around ----(b)(4)----. We would expect you to perform a re-validation of your ----(b)(4)---- process for this product after production was suspended for an extended period of time (over ---(b)(4)--- in this case). Resuming (b)(4) audits after ---(b)(4)--- of non-production is not sufficient. In addition, validation of all other processing steps for this product is required prior to resuming production, as discussed previously.

Your response stated that for all other products, you performed ----(b)(4)--- audits every cumulative production (b)(4). We disagree with your response. For example, our review of your production cycle records found that the Dembone family products were manufactured between February 2010 and February 2012 ((b)(4) production cycles). (b)(4) audits were performed only three times during this period.

Your response to Observation 4.B. references the -----
----- (b)(4) -----
----- . You included a statement from the report that, "-----

---(b)(4)-----
-----." You stated that this was
standardized practice used to validate your ----(b)(4)---- process. However, we note that this
same industry guidance also states, "-----
----- (b)(4) -----
-----." This was not
addressed as part of your validation. We acknowledge your commitment to perform
validation of your --- (b)(4) --- process using anaerobic organisms, however your response did
not address the HCT/Ps that your firm has manufactured since March 19, 2009, using a
terminal sterilization process that was not validated in accordance with 21 CFR 1271.

5. Your response to Observation 5 did not provide adequate justification for not performing environmental monitoring in Room (b)(4), where processing steps take place.
6. Your response to Observation 6 did not address the inadequate facility conditions observed during the inspection or how your corrective actions will prevent the recurrence of similar deviations to ensure aseptic processing operations. In regard to the establishment of an SOP for changing the air inlet filter on the ----(b)(4)---- on an --(b)(4)-- basis, you provided no justification for this --(b)(4)-- replacement schedule. Please explain how you determined that --(b)(4)-- replacement of the filter was appropriate.

7. In regard to Observation 7.A., your corrective actions do not address how you intend to prevent recurrence of this deviation.

Your response to Observation 7.B. addresses the scheduled inspection by the manufacturer of the -----(b)(4)----- precision saw units, “to determine if the observations reported by Inspectors can compromise equipment reliability and function.” We remind you that under 21 CFR 1271.200(b), you must establish and maintain procedures for cleaning, sanitizing, and maintaining equipment to prevent contamination or cross-contamination, accidental exposure of HCT/Ps to communicable disease agents, and other events that could reasonably be expected to result in the introduction, transmission, or spread of communicable diseases. Your response also did not discuss the unidentified material in the lid of one saw or the cracks found in the lid of the other saw. In addition, you did not address how you intend to maintain your equipment to prevent contamination of HCT/Ps during processing or how the inspection by the equipment manufacturer will address the violations cited.

8. In regard to Observation 8.a., i-iii, 8.b., and 8.c., we acknowledge that your response states that repairs were made to the roof, ceiling, and light fixture in your processing areas. The adequacy of these corrective actions will need to be confirmed during the next inspection of your facility.

In your response to Observation 8.d., you did not indicate whether the ceiling in Room (b)(4) was repaired.

9. Your response to Observation 10 states that in the future, if loss of vacuum should occur, you will report such deviations to FDA. However, to date, you have not submitted an HCT/P Deviation Report to FDA, as required under 21 CFR 1271.350(b)(2), for the deviation cited in this observation.
10. Your response to Observation 11 states that, “the reason working bench surfaces were not sanitized is that these were covered with -----(b)(4)----- and tissue were processed on the same.” We note that your SOPs appear to be in conflict regarding this practice. Your SOP, “Facility -(b)(4)- Cleaning Protocol” states, “facility shall be maintained in a clean and sanitary manner by subjecting it to -(b)(4)- cleaning and sanitation procedure during the working days. -(b)(4)- cleaning and sanitation procedure consists of wiping surfaces with -----(b)(4)-----.” However, page 24 of your SOP manual, under the “Reagents and Supplies-General” section, states, “All surfaces coming in contact with the tissues intended for transplantation are covered with ----(b)(4)---- or disinfected.” Under 21 CFR 1271.190(b), you must establish and follow a cleaning program for your facility, adequate to prevent the introduction, transmission, or spread of communicable disease. Your practice of covering surfaces with ----(b)(4)---- is not sufficient.
11. In regard to Observation 12, we acknowledge that you have established an SOP for evaluating the suitability of HCT/Ps returned to Pacific Coast Tissue Bank by your consignees. However, your response does not address the 84 HCT/Ps that were returned between 3/31/10 and 4/5/12, for which there was no evaluation for the presence of microorganisms, damage, or contamination.

12. Your corrective actions in response to Observation 14 do not address how you will prevent recurrence of this deviation.
13. In your response to Observation 15, you stated that "Copies of Quality Assurance Review file, External Audit file and Corrective Actions are maintained by PCTB. If requested to do so we will be glad to send copies of the same to the District Director, FDA." Please submit the copies of the files you referenced to FDA.

This letter confirms the telephone conversation on November 5, 2012, in which notice was given that, pursuant to 21 CFR 1271.440(a)(3), upon receipt of this Order, you must:

1. Immediately cease all manufacturing of HCT/Ps until compliance with the regulations in 21 CFR 1271 has been achieved and you have been provided written authorization from FDA to resume operations. Under 21 CFR 1271.3(e) manufacture means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any HCT/P, and the screening or testing of the HCT/P donor;
2. Destroy all HCT/Ps that are in your possession; and
3. Within five (5) working days from the date of receipt of this order, recall and destroy all HCT/Ps distributed since March 19, 2009, the date you began manufacturing HCT/Ps.

Instructions were given at the time of the telephone conversation to cease manufacturing, recall, and destroy HCT/Ps. You may not resume operations without prior written authorization from FDA. Before FDA will issue such an authorization, you must ensure compliance with FDA's regulations in 21 CFR Part 1271 – including, but not limited to, the Donor Eligibility and current Good Tissue Practice requirements in 21 CFR 1271, Subpart C and Subpart D. Any shipment of HCT/Ps in violation of this order constitutes a violation of Section 368 of the PHS Act [42 USC 271], for which criminal penalties may be imposed.

Within five (5) working days from the receipt of this Order to Cease Manufacturing and Recall and Destroy, you may request a hearing on the matter in accordance with 21 CFR Part 16 (copy attached), to Mary A. Malarkey, Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, 1401 Rockville Pike, HFM-600, Rockville, MD 20852 (telephone: 301-827-6190). A request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that warrants a hearing. Pursuant to 21 CFR 16.26, a request for a hearing may be denied, in whole or in part, if the Commissioner or her delegate determines that no genuine and substantial issue of fact has been raised by the material submitted. A hearing will not be granted on issues of policy or law. Written notice of a determination of summary judgment will be provided, explaining the reasons for denial of the hearing. Should you need additional time in which to request a hearing, please notify us immediately, in writing, of your request for additional time.

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Failure to request a hearing within the specified time period constitutes a waiver of the right to a hearing. You may also wish to inform yourself with respect to the agency's guidelines regarding electronic media coverage of its administrative proceedings, which can be found at 21 CFR 10, Subpart C.

Sincerely,

Karen Midthun, M.D.
Director
Center for Biologics Evaluation and Research

Effective Date: _____ Time: _____

Attachments (2)
21 CFR Part 1271
21 CFR Part 16